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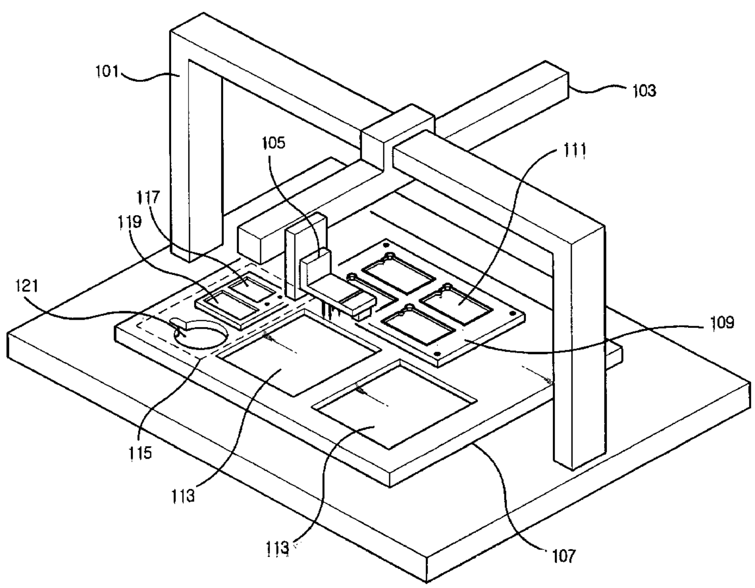
(54) **Title:** HIGH PRECISION AND INTELLECTUAL BIOCHIP ARRAYER HAVING FUNCTION OF RESPOTTING



(57) **Abstract:** The present invention relates to a bio-chip arrayer. The bio-chip arrayer in accordance with the present invention comprises a substrate retaining stand which is separable from the bio-chip arrayer and has a plurality of substrate retaining grooves, wherein each substrate retaining groove includes a retaining edge, a retaining protuberance and a aligning boss for inserting tightly a bio-chip substrate. By using the bio-chip arrayer in accordance with the present invention, the bio-chip substrate may be arrayed on a same position every time. Also, the bio-chip substrate may be re-arrayed by setting up easily a central position and co-ordinates.

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HIGH PRECISION AND INTELLECTUAL BIOCHIP ARRAYER HAVING FUNCTION OF RESPOTTING

Technical Field

The present invention relates to a high precision and intellectual biochip arrayer with a respotting function, and more particularly to a biochip arrayer capable of precise respotting through a substrate, retaining grooves formed thereon for accurately retuning a biochip substrate to its exact previous position, or an optical sensor for precisely recognizing a reference position so as to define a central position and a coordinate system.

Also, to achieve higher efficiency and wider application, the present invention relates to a biochip arrayer having a function of precise respotting, comprising an optical sensor used for recognizing an identifier attached to a biochip so as to extract information from said identifier such as the type of biochip spot, the procedure used to deposit the spot, the arrangement of the spot array, the reference position, the spot size, and the intervals between spots from a database corresponding to the identifier.

Background Art

A biological chip or a biochip is called a biological array. The concept of a biochip is commonly understood today. A biochip has a substrate having biological material such as nucleic acid. A deoxyribonucleic acid (DNA) chip is one example of a well-known

biochip. The DNA chip has a substrate with DNA fixed thereon. A protein chip is another example of a biochip and has a substrate with protein formed thereon.

A biochip operates on the basis of the interaction between a target molecule and a fixed molecule attached to a substrate. For example, the DNA chip operates by means of a complementary combination of oligonucleotides fixed to a substrate and the bases of the DNA existing in the sample. Alternatively, a protein chip operates by means of the interaction between protein molecules such as those found in the antigen-antibody bond or the ligand-accepter combination.

Because of the recent improvements in DNA sequencing technology, the gene arrangements of various living things from bacteria to humans are being mapped and vast quantities of information about the configuration and function of the human genome will be understood due to the accomplishments of the Human Genome Project. However, it is difficult to research the hundreds pieces of genetic information newly discovered each day by means of conventional research methods since these methods require much time and efforts, therefore, faster and more precise technology is required for researching numerous genetic databases at the same time.

Therefore, in order to efficiently research genetic information, a DNA chip has been developed that combines the conventional biological technology, mechanical automation, and electronic control technology. The DNA chip means the substrate on which a plurality of DNA is stored at high-density levels, awaiting retrieval.

Conventional biological researching techniques only study a small number of samples at a time. For example, Southern Blot, Northern Blot, mutation retrieval and DNA sequencing. However, many genes can be more efficiently and automatically analyzed at once due to the development of the DNA chip.

The DNA chip has many advantages. Enormous amounts of data can be obtained through a single experiment. Manipulation of the DNA chip and mechanical automation can easily be accomplished, so research of DNA chips may replace conventional biological researching methods. Also, the DNA chip can be widely applied to various fields such as the analysis of the function of genes, identifying genes responsible for causing diseases like cancer, gene therapy, the quarantine of animals and plants, the testing of food, the development of new medicines, the retrieval of mutated genes, the analysis of the arrangement of bases, the testing of tissues, identifying disease causing microorganisms, forensic medicine, etc.

There are four types of DNA chips, differentiated by the manufacturing method used to fix the oligonucleotides onto their substrates. They are as follows:

1) Pin micro-array Type: wherein DNA is implanted at identical positions using a pin,

2) Ink Jet Type: wherein genes contained in a cartridge are injected onto a substrate by means of electrical force,

3) Photolithography Type: wherein the DNA is directly composed on a substrate

by means of photosensitive chemicals, and

4) Electronic array Type: wherein the DNA representing a minus (-) charge is attached to a predetermined position on a substrate while the material representing a plus (+) charge is coated.

Also, a fluorescent reader and an electric signal reader are developed as the apparatus used to collect data contained on a DNA chip.

As it is described above, though many technologies surrounding DNA chips have been developed for genetic research, advances in the use of DNA chips for the configuration of an automated disease diagnosis system have not yet been sufficiently developed.

The immunity diagnosis method of identifying diseases ranges from the utilization of the blood corpuscle coagulation reagent to the chemical luminescence immunity measurement method through the radioactive rays immunity measurement method and the enzyme immunity measurement method.

According to conventional diagnosis methods, after an antigen is fixed and reacted with an antibody in a sample (mainly, serum) obtained from an entity, the antigen-antibody reaction is measured by using a secondary antigen composed of a radioactive indicator, an enzyme and a fluorescent material. The conventional method, however, can measure only a few samples at a time as discussed previously in the gene analysis method. Hence, it is difficult to perform simultaneous diagnosis of various diseases, diagnosis for multiple

persons, or diagnosis of various diseases in multiple persons. Also, the conventional methods require, much cost and time since the analysis procedures thereof are not automated.

Protein chips comprises protein fixed onto a substrate while DNA chips has DNA fixed onto a substrate. Also, the bound reaction of a protein chip requires multiple reactions composed of a reaction between an antigen and a primary antibody and a reaction between the primary antibody and a secondary antibody. In addition, the separation/combination of the protein chip and the movement of the protein chip can occur when each reaction transpires inside a chemical reactor.

In general, it is understood that antigen proteins or peptides have various electrical properties depending on their type and configuration, and are larger than that of the DNA spot, while DNA has a minus charge and DNA spots range from 15 to 25 bases to about 500bp. Also, proteins are fixed onto a substrate without interfering with, or deforming, the structure of antigen. Considering such parameters, the method for fixing a protein onto a substrate is different from that used for DNA, so it is necessary that each antigen protein be fixed within an optimum range under fixing conditions optimized to facilitate mass production, and utilizing a detecting procedure capable of ensuring that various antigen proteins are fixed onto the same substrate, unlike the procedure employed to fix all the DNA having similar properties onto the same substrate.

In addition, to precisely accomplish a reaction on the surface of the minute

substrate, great precision must be taken in placing the protein chip when using the immunity analysis method for achieving multiple reactions. Therefore, it is important that the accurate position is chosen whereon to dot the sample in each reaction step.

The conventional biochip arrayer is disclosed as Genosensor Arrays manufactured by Genosensor Co. in the U.S.A., Biochip Arrayer manufactured by Parkard Instrument Co. in the U.S.A., Micromax Microarray made by NEN Co. in the U.S.A., and Q array manufactured by Genetix Co. in the England.

However, the conventional biochip arrayer may not cope with the separation/combination of the chip and the movement of the chip such as the protein chip because the conventional biochip arrayer can applied to the DNA chip only. The conventional biochip arrayer is rarely used today except for experimental purpose.

Also, the conventional biochip arrayer often does not cope with deformations and errors on the biochip substrate. That is, the conventional biochip arrayer may not overcome a minute error or deformation generated during the manufacturing process of the biochip substrate and will not always dot the sample correctly in each reaction step.

Furthermore, the conventional biochip arrayer may not ensure a precise alignment of the biochip in the biochip arrayer depending on how the sample is fixed to the biochip at the manufacturer. A protein chip should be precisely aligned while the DNA chip does not require such precise alignment.

The conventional biochip arrayer has a substrate retaining stand fixed onto the bed

thereof, preventing the substrate retaining stand from being easily maintained or repaired.

Disclosure of the Invention

The present invention is intended to overcome the above-described disadvantages. Therefore, it is an object of the present invention to provide a biochip arrayer that can be applied to all kinds of biochips such as a deoxyribonucleic acid chip or a protein chip by using a multiple spindle transfer system.

It is another object of the present invention to provide a biochip arrayer having a substrate retaining-groove so as to align a biochip substrate to the same position every times.

It is still another object of the present invention to provide a biochip arrayer having an aligning boss formed on the substrate retaining-groove for setting a central position and a coordinate system for the biochip substrate.

It is still another object of the present invention to provide a biochip arrayer having a substrate retaining stand including a plurality of substrate retaining-grooves on which aligning bosses are formed in order to set central positions and coordinates systems for a plurality of biochip substrates, respectively.

It is still another object of the present invention to provide a biochip arrayer having an optical sensor for recognizing predetermined reference points previously indicated on a biochip substrate so as to set a central position and a coordinate system for the biochip

substrate.

It is still another object of the present invention to provide a biochip arrayer that is highly efficient and widely applicable due to its the optical sensor because its optical sensor recognizes an identifier on a biochip substrate to which a reference point has been previously attached, thereby utilizing many pieces of information such as the types of samples on the biochip, the procedure and an alignment of a spot array, the manufacturer and diagnosis dates of the biochip, the position of the reference points, and sizes and intervals of spots after retrieving the information from a database corresponding to the identifier.

It is still another object of the present invention to provide a biochip arrayer having a substrate retaining stand which can be formed separately, thereby facilitating ease of maintenance or repair done to the substrate retaining stand.

It is still another object of the present invention to provide a biochip arrayer having different spots for samples, thereby facilitating simple diagnosis of samples.

To accomplish the objects of the present invention according to one aspect of the present invention, there is provided a biochip arrayer comprising a substrate retaining stand having at least one substrate retaining groove for fixing a biochip substrate inserted into the substrate retaining groove and a bed including at least one well plate retaining groove for fixing a well plate, wherein the substrate retaining groove comprises a first side for supporting the biochip substrate by two points or one line, a second side for supporting the

biochip substrate by one point or one line, and an aligning boss for receiving a portion of the biochip substrate wherein the biochip substrate supported by the two points means the biochip's substrate is supported by two retaining protuberances that corresponded to the two points and are formed at predetermined positions on the first side and wherein the biochip substrate supported by the one point means the biochips substrate is supported by a retaining protuberance corresponding to the one point and is formed at a predetermined position on the second side

According to one preferred embodiment of the present invention, the first side crosses substantially at a right angle or a predetermined angle, with the second side and the aligning boss is formed between the first side and the second side.

According to another preferred embodiment of the present invention, the substrate retaining groove further comprises push portions respectively formed on a third side and a fourth side corresponding to the first side and the fourth side, respectively. At such time, the push portions respectively support the biochip substrate so that the biochip substrate is inserted and fixed into the substrate-retaining groove. The push portions are springs or elastic members, respectively, or a plurality of springs or elastic members, respectively.

In still another preferred embodiment of the present invention, the aligning boss has a central position for indicating a coordinate point on the biochip substrate. In this case, the central position is indicated by aligning a home position setting pin, a pin head and the aligning boss.

According to still another preferred embodiment of the present invention, the substrate-retaining stand is combined separately with the bed. The bed comprises a washing portion for washing a sample remaining on a probe or the container receiving the sample.

To accomplish the objects of the present invention according to another aspect of the present invention, there is provided a method for dotting a biochip wherein a sample is dotted onto a biochip substrate on a biochip array wherein the first sample has the same size as the first spot and has been previously dotted so as to be formed onto the biochip substrate using a biochip arrayer from a manufacturer, which comprises the steps of disposing the probe mounting part of a biochip arrayer that has been used by a user for dotting a second sample onto the first spot of the biochip substrate by using the biochip arrayer of the user, and dotting the second sample onto a second spot corresponding to the second sample by using the biochip arrayer of the user, wherein the second spot has a different size than the first spot.

According to one preferred embodiment of the present invention, the step of dotting the second sample onto the second spot is performed by adjusting the size of a second probe corresponding to the second spot to differ from the size of the first probe that corresponds to the first spot, and then dotting the second sample.

According to another preferred embodiment of the present invention, the second spot is smaller than the first spot when the first spot is an antigen and the second spot is an

antibody.

To accomplish the objects of the present invention according to still another aspect of the present invention, there is provided a method for manufacturing a biochip by using a biochip array comprising the step of recognizing a biochip identifier indicated on a biochip substrate, extracting biochip information corresponding to the biochip identifier from a built-in database wherein the biochip information includes at least one selected from the group consisting of the total number of spots, the alignment of the spots, the contents of the spots, the sizes of the spots, the intervals between the spots, the position of a reference spot and the operating procedure of the biochip arrayer, and dotting the contents of the spots onto the biochip substrate by using the biochip information.

According to on preferred embodiment of the present invention, the biochip identifier is recognized from a bar code attached to the biochip substrate. In this case, the bar code is a first dimension bar code, a second dimension bar code or a third dimension bar code.

To accomplish the objects of the present invention according to still another aspect of the present invention, there is provided a biochip arrayer comprising an optical sensor for recognizing at least one reference point previously indicated on a biochip substrate, a memory storage and retrieval a program, and a processor combined with the memory to execute the program, wherein the processor executes in accordance with the program the step of setting a central position and a coordinate system for the biochip substrate to be

retrieved by recognizing at least one reference point and setting coordinates of spots to be retrieved by using the set central position and the coordinate system.

According to the preferred embodiment of the present invention, the reference point comprises a first reference value corresponding to the central position, a second reference value corresponding to an x-axis and a third reference value corresponding a y-axis.

In another preferred embodiment of the present invention, the optical sensor is an image detecting element or a position detecting element.

To accomplish the objects of the present invention according to still another aspect of the present invention, there is provided a biochip arrayer comprising an optical sensor for recognizing at least one reference point previously indicated on a biochip substrate, a memory storage and retrieval a program, and a processor combined with the memory to execute the program, wherein the processor executes in accordance with the program the step of setting a central position and a coordinate system on the biochip substrate to be read by the recognition of at least one reference point, the recognition of positions of spots by using the set central position, the coordinate system and coordinates of the spots wherein the coordinates of the spots are previously known, and controlling the dotting of sample in correspondence with the recognized positions of the spots.

Brief Description of the Drawings

The above objects and other advantages of the present invention will become more apparent by detailed description of the preferred embodiments thereof with reference to the attached drawings in which:

FIG. 1 is a perspective view showing a biochip arrayer according to one preferred embodiment of the present invention;

FIG. 2 is a schematic view illustrating a configuration of a control system by using an optical sensor in the biochip arrayer according to one preferred embodiment of the present invention;

FIG. 3 is an enlarged side view showing a portion of the biochip arrayer according to one preferred embodiment of the present invention;

FIG. 4 is an exploded perspective view showing the bed in FIG. 3 according to one preferred embodiment of the present invention;

FIG. 5 is a perspective view showing a substrate-retaining stand according to one preferred embodiment of the present invention;

FIGS. 6A is a plane view illustrating a substrate-retaining groove according to one preferred embodiment of the present invention;

FIG. 6B is a plane view illustrating a substrate-retaining groove according to another preferred embodiment of the present invention;

FIG. 6C is a plane view illustrating a substrate-retaining groove according to still

another preferred embodiment of the present invention;

FIG. 6D is a plane view illustrating a substrate-retaining groove according to still another preferred embodiment of the present invention;

FIG. 6E is a side view illustrating a spring functioning as a push member in FIGS. 6B to 6D according to one preferred embodiment of the present invention;

FIG. 6F is a side view illustrating an elastic member functioning as a push member in FIGS. 6B to 6D according to another preferred embodiment of the present invention;

FIG. 7 is a perspective view illustrating a method for setting a portion of an align boss of a substrate retaining groove to a central position according to one preferred embodiment of the present invention;

FIG. 8 is a perspective view illustrating a method for aligning a biochip substrate by using an optical sensor according to one preferred embodiment of the present invention;

FIG. 9 is a plane view for showing a biochip on which a reference point is indicated according to one preferred embodiment of the present invention;

FIG. 10A is a flow chart illustrating a method for respotting a biochip arrayer by using an optical sensor according to one preferred embodiment of the present invention;

FIG. 10B is a schematic plane view illustrating a reference representation according to one preferred embodiment of the present invention;

FIG. 11 is a flow chart illustrating a method for manufacturing a biochip with high precision and intellectual biochip arrayer recognizing a biochip identifier according to one

preferred embodiment of the present invention;

FIG. 12 is a schematic view illustrating a database retrieving biochip information corresponding to a biochip identifier according to one preferred embodiment of the present invention;

FIG. 13 is a plane view illustrating a method for the calibration of a bed according to one preferred embodiment of the present invention;

FIG. 14A is a cross-sectional view illustrating a method for adjusting the height of a third supporting point according to one preferred embodiment of the present invention;

FIG. 14B is a cross-sectional view illustrating a method for adjusting heights and y-axis directions of a first and a second supporting points according to one preferred embodiment of the present invention; and

FIG. 15 is a plane view illustrating a method for adjusting the y-axis direction of a bed according to one preferred embodiment of the present invention.

Best Modes for carrying out the Invention

Hereinafter, preferred embodiments of the present invention will be described in more detail with reference to the accompanying drawings, but it is understood that the present invention should not be limited to the following embodiments.

In the preferred embodiment of the present invention, a biochip is representative of various biological chips including a deoxyribonucleic acid chip, a protein chip, a

ribonucleic acid chip and so on. However, the protein chip will be described as the biochip hereinafter.

The manufacturing and utilizing processes of the biochip will be described as follows.

First, a primary protein chip is formed by dotting an antigen onto a biochip arrayer for a manufacturer. Then, the primary protein chip is dried in a reaction apparatus maintained at a predetermined temperature and humidity level. In this case, each spot on the primary protein chip can be identical or different. For example, a portion of the primary protein chip can hold a human immunodeficiency virus (HIV) antigen, another portion of the primary protein chip can hold a hepatitis B virus (HBV) antigen and the other portion the primary protein chip can hold a hepatitis C virus (HCV) antigen.

The primary protein chip is provided to a consumer such as a hospital. The consumer dots an antigen such as the blood or body fluids of a patient to be tested onto the primary protein chip to form a secondary protein chip in the biochip arrayer of the consumer. At that time, the spot of a previously manufactured protein chip should be placed at an identical position to the spot of the biochip in the arrayer of the consumer. That is, it is important that the antigen is accurately dotted to the corresponding spot of the primary protein chip that is next to be realigned. Then, the secondary protein chip is reacted in the reaction apparatus.

Subsequently, fluorescenin isothiocyanate, a fluorescent material, is dotted onto

the secondary protein chip after the user installs the reacted secondary protein chip into the biochip arrayer of the consumer. In this case, the realignment is required to facilitate precise respotting.

Then, the result of the reaction can be extracted using a biochip reader, thereby accomplishing the diagnosis.

FIG. 1 is a perspective view showing a biochip arrayer according to one preferred embodiment of the present invention.

Referring to FIG. 1, the biochip arrayer comprises a transfer part 103 including a probe mounting portion 103 whereon at least one probe is mounted, a transfer shaft 101 for supporting the transfer part 103, a bed 105 and a central control part (not shown) for controlling those elements. The central control part will be explained with reference to FIG. 2. In this case, the transfer shaft 101 and the transfer part 103 can execute a multiple spindle transfer under the control of the central control part. Also, the probe and the probe-mounting portion 105 will be described.

A substrate-retaining stand 109 having a plurality of substrate retaining grooves 111 for fixing several biochip substrates formed onto the bed 107. A washing portion 117 for washing the probe or a container for receiving samples is formed on the bed 107 and a washing member 115 having a vacuum suction portion 119 and an ultrasonic washer 121 is formed on the bed 107. Also, at least one well plate-retaining groove 113 having at least one well plate formed onto the bed 107.

The central control part, having a controller (not shown), is in charge of a relative position control that determines the relative positions between the probe mounting portion 105, the substrate-retaining groove 111, the well plate retaining groove 113 and the washing member through a multiple spindle transfer system. At that time, the multiple spindle transfer system can be applied to all various values of the relative position control as well as to the case wherein the bed 107 is fixed.

FIG. 2 is a schematic view illustrating a configuration of a control system using an optical sensor in the biochip arrayer according to one preferred embodiment of the present invention.

Referring to FIG. 2, the central control part 201 receives a biochip identifier from an optical sensor and uses the identifier to recognize a chip 207 and receives a reference point position from an optical sensor, the optical sensor used for recognizing a reference point 209, and then the central control part 201 sends control signals corresponding to the biochip identifier and the reference point position to an x-axis transfer driver 213, a y-axis transfer driver 217, a z-axis transfer driver 221, an ultrasonic driver 223, a vacuum valve driver 225 and a pump driver 227, respectively. The optical sensor used for recognizing a chip 207 can be composed of one optical sensor and the optical sensor for recognizing a reference point 209 can also be composed of one optical sensor. The optical sensor for recognizing a chip 207 recognizes the biochip identifier from a bar code attached to the biochip.

The central control part 201 includes a standard personal computer 203 and the controller 205. The controller 205 generates the control signals after the controller 205 receives a communication command and other optical sensor information from the personal computer 203. Also, the controller 205 receives state information about each element and transfers the state information to the personal computer 203 or an upper controller (not shown).

The x-axis transfer driver 213, the y-axis transfer driver 217 and the z-axis transfer driver 221 respectively control an x-axis motor 211, a y-axis motor 215 and a z-axis motor 219 so as to execute the position control after the x-axis transfer driver 213, the y-axis transfer driver 217, the z-axis transfer driver 221 receive the control signal from the central control part 201.

Also, the ultrasonic driver 223 performs washing by generating ultrasonic waves in the ultrasonic washer 121 after the ultrasonic driver 223 receives the control signal from the central control part 201. Furthermore, the vacuum valve driver 225 performs washing by means of a vacuum produced in the vacuum suction portion 119 and the pump driver 227 executes washing by pumping water into the solution washing portion 117.

FIG. 3 is an enlarged side view showing a portion of the biochip arrayer according to one preferred embodiment of the present invention.

As shown in FIG. 3, the biochip arrayer comprises a bed 107, a plurality of probes 301 and a probe-mounting member 105.

The probe-mounting member 105 can rotate and move to the right or left. The probe-mounting member 105 can be established as a general robot arm. In this case, the probe-mounting member 105 should be bound so that the probe 301 only moves in an upward or downward motion along the z-axis.

The probe 301 is shaped like a pin having thin and long dimensions so as to spot a sample onto a biochip substrate. The sample is attached to an end of the probe 301 to be spotted onto the biochip substrate.

When the biochip substrate is that of a protein chip, the biochip substrate is a solid plate whose spots are fixed with a number of proteins that are affixed in order. Preferably, the surface of the biochip is coated.

The solid plate can be composed of glass, deformed silicon, polymer or gel such as tetraflouroethylene, polystyrene or polypropylene. Preferably, the surface of the substrate can be coated with a polymer, plastic resin, carbohydrate, silica, silica derivative, carbon, metal or glass.

The biochip substrate not only supports the samples but also provides the space wherein the reaction between the fixed sample and a target sample occurs. The dimensions, the size and the shape of the biochip substrate can be varied in accordance with the purpose of the analysis and devices employed such as a liquid treating device and a reading wand. Also, the position of the biochip substrate whereon the samples are fixed can be varied according to the purpose of the analysis and the types of devices employed.

The bed 107 has the biochip substrate affixed thereon and the samples are spotted onto the biochip. The bed 107 will described in detail with reference to FIG. 4.

FIG. 4 is an exploded perspective view showing the bed in FIG. 3 according to one preferred embodiment of the present invention.

Referring to FIG. 4, the bed 107 includes the substrate retaining stand 109 having a plurality of substrate retaining grooves 111, the container washing portion 117, the washing member 115 (see FIG. 1) having the vacuum suction portion 119 and the ultrasonic washer 121, and the well plate retaining groove 113 whereon at least one well plate is fixed. The substrate of the substrate retaining groove 111 and the substrate retaining stand 109 means the biochip substrate.

The substrate-retaining stand 109 is separable from the bed 107. The substrate-retaining stand 109 can be tightly inserted into a groove formed on a portion of the bed 107 when the groove is formed to receive a portion of the substrate-retaining stand 109. Also, the substrate-retaining stand 109 can be combined with the bed 107 by means of a screw combination. Furthermore, the substrate-retaining stand 109 can be combined with the bed 107 by means of a magnet combination.

Since the substrate-retaining stand 109 is combined to, but separately from the bed 107, the substrate retaining stand 109 alone can be separated and changed without it being necessary to also change the bed 107 when the substrate retaining stand 109 is damaged. Because of this future, the substrate-retaining stand 109 can be easily maintained.

The number of biochip substrates to be mounted can be easily varied because the substrate-retaining stand 109 can be separated from the bed 107 and the number of the substrate-retaining groove 111 can be varied. For example, the number of the biochip substrates can be changed from four to eight when the substrate-retaining stand 109 having four substrate-retaining grooves 111 is exchanged with the substrate-retaining stand 109 having eight substrate-retaining grooves 111.

The substrate-retaining groove 111 will be explained with reference to FIGS. 6A to 6F.

The washing member 115 (see FIG. 1) washes the samples remaining on the probe and the container receiving the samples after the samples are spotted onto the biochip. The container washing portion 117 washes the remaining samples and the container with water. The vacuum suction portion 119 washes the remaining samples and the container using the vacuum suction. The ultrasonic washer 121 washes the remaining samples and the container by using the ultrasonic wave.

The well plate-retaining groove 113 retrieves the samples fixed onto the biochip where the probe of the probe-mounting portion 105 is inserted into the substrate-retaining groove 111 to be fixed.

FIG. 5 is a perspective view showing a substrate-retaining stand according to one preferred embodiment of the present invention.

As shown in FIG. 5, four substrate-retaining grooves 111 are preferably formed on

the substrate-retaining stand 109. The substrate-retaining grooves 111 can be adjusted to accommodate the size of the biochip substrate.

FIGS. 6A is a plane view illustrating a substrate-retaining groove according to one preferred embodiment of the present invention.

Referring to FIG. 6A, the substrate-retaining groove 111 includes a retaining edge 603, a retaining protuberance 607 and an aligning boss 605.

When a biochip substrate 601 is inserted into the substrate-retaining groove 111, the biochip substrate 601 is supported at one point by the retaining protuberance 607 and is supported along one edge by the retaining edge 603.

To fix all biochip substrates 601 at the same position having the same shape, the retaining edge 603 and the retaining protuberance 607 are formed on the substrate retaining groove 111 since biochip substrates 601 do not always have the same dimensions and shape after the biochip substrates 601 are manufactured. It is preferable that one portion of the substrate-retaining groove 111 corresponding to the retaining edge 603 is substantially at a right angle with the other portion of the substrate-retaining groove 111 corresponding to the retaining protuberance 607.

The aligning boss 605 has the shape of a circle so as to receive a corner of the biochip substrate 601. Also, the aligning boss 605 performs the function of alignment.

In another preferred embodiment of the present invention, the aligning boss 605 can have various shapes such as an ellipse, a triangle or a tetrahedron, thereby enabling the

corner of the biochip substrate 601 to be received.

FIG. 6B is a plane view illustrating a substrate-retaining groove according to another preferred embodiment of the present invention.

Though the substrate-retaining groove 111 is substantially identical to that in FIG. 6A, push members 609 are formed on the sides of the retaining edge 603 and the retaining protuberance 607.

The push members 609 tightly hold the biochip substrate 601 when the biochip substrate 601 is inserted into the substrate-retaining groove 111. At that time, force is demanded to tightly insert the biochip substrate 601.

The push members 609 are formed on the substrate-retaining groove 111, but the push members 609 can be formed in such a way to enable them be separated from the substrate retaining groove 111 according to another preferred embodiment of the present invention.

FIG. 6C is a plane view illustrating a substrate-retaining groove according to still another preferred embodiment of the present invention.

Referring to FIG. 6C, though the substrate-retaining groove 111 is similar to that in FIG. 6B, the substrate-retaining groove 111 includes two retaining protuberances 607 instead of the retaining edge 603 to support the biochip substrate 601 along one line as does the retaining edge 603. Two edges of the two retaining protuberances 607 together support the biochip substrate 601 along one line though the edges of the two retaining

protuberance 607 are respectively support the biochip substrate 601 at one point.

FIG. 6D is a plane view for illustrating a substrate-retaining groove according to still another preferred embodiment of the present invention.

As shown in FIG. 6D, though the substrate-retaining groove 111 is similar to that in FIG. 6B, the retaining edge 603 is formed instead of the retaining protuberance 607. Hence, the substrate-retaining groove 111 includes two retaining edges 603 respectively supporting the biochip substrate 601 along one line.

FIG. 6E is a side view illustrating a spring as a push member in FIGS. 6B to 6D according to one preferred embodiment of the present invention.

Referring to FIG. 6E, the spring 611 tension presses the biochip substrate 601 firmly to the retaining edge 603 and the retaining protuberance 607 with a predetermined force.

The push member 609 can be composed of a plurality of springs 611. However, the force pushing the biochip substrate 601 from one side of the retaining edge 603 should be divided into two components so as to prevent the biochip substrate 601 from rotating at the retaining edge 603. Also, the force pushing the biochip substrate 601 from one side of the retaining protuberance 607 should be directed towards the retaining protuberance 607.

FIG. 6F is a side view illustrating an elastic member as a push member in FIGS. 6B to 6D according to another preferred embodiment of the present invention.

Referring to FIG. 6F, the elastic member 613 generates a predetermined elastic

force in one direction along the retaining edge 603 and the retaining protuberance 607 so that the biochip substrate 601 is tightly held to the substrate-retaining groove 111 when the biochip substrate 601 is inserted into the substrate-retaining groove 111.

The push member can be composed of a plurality of elastic members 613 similar in function to the plurality of the springs 611. Also, the force pushing the biochip substrate 601 from one side of the retaining edge 603 should be divided into two components so as to prevent the biochip substrate 601 from rotating at the retaining edge 603. That is, the force should be provided without generating momentum at one end of the biochip substrate 601. Also, the force pushing the biochip substrate 601 from one side of the retaining protuberance 607 should be directed toward the retaining protuberance 607.

The push member 609 is also fixed to the biochip substrate 601 at the same position and with the same shape since the biochip substrate 601 does not always have the same dimension and the same shape after the biochip substrate 601 is manufactured.

Referring to FIG. 5 again, a plurality of substrate retaining grooves 111 are formed on the substrate retaining stand 109 and a plurality of biochip substrates 601 corresponding to the substrate retaining grooves 111 are inserted into the substrate retaining grooves 111.

In this case, when a portion of one substrate retaining groove 111 from among the substrate retaining grooves 111 is set as a central position and the positions of the other substrate retaining grooves 111 are relatively set to the basis of the central position, the position of the biochip substrate 601 may be difficult to discriminate due to transfer error

or thermal deformation error.

Therefore, according to the present invention, a portion of the aligning boss 605 between the substrate-retaining grooves 111 is specifically set to be the central position so that the positions of the biochip substrates 101 can be determined respectively as positions to the central position, thereby minimizing the effect due to transfer error and thermal deformation error. Namely, all the aligning bosses 605 of the substrate retaining grooves 111 retain respectively their central positions so that different coordinate systems are set respectively for each biochip substrates 601.

The method for setting portions of the aligning bosses 605 of substrate-retaining grooves 111 to central positions will be described with reference to FIG. 7.

FIG. 7 is a perspective view for illustrating a method for setting a portion of an aligning boss of a substrate-retaining groove to a central position according to one preferred embodiment of the present invention.

Referring to FIG. 7, after the pin head 703 is transferred so that the home position setting pin 701 attachable to the probe mounting member 105 (see FIG. 1) is inserted into a circular groove of the aligning boss 605 of the substrate-retaining groove 111 and into a circular groove of the pin head 703, the coordinate is thereby set as the home position of the biochip substrate 701.

When the above-described work is repeated for each biochip substrate 601, different coordinate systems can be set for all the biochip substrates 601, thereby

minimizing the affect of transfer errors of the apparatus and thermal deformation errors on the biochip substrate 601.

The biochip array dots the samples by using the central position and the coordinate system set respectively for each biochip substrate 601.

FIG. 8 is a perspective view illustrating a method for aligning a biochip substrate by using an optical sensor according to one preferred embodiment of the present invention.

As shown in FIG. 8, the optical sensor 801 is attached to the probe mounting member 105 (see FIG. 1) to detect the reference point previously indicated on the biochip substrate 805, thereby setting the central position and the coordinate system of the biochip substrate 805.

In one preferred embodiment of the present invention, the optical sensor 801 can be an image detecting element or a position detecting element. Preferably, the optical sensor 801 can be a charged coupled device (CCD) camera. Also, the reference point previously indicated on the biochip substrate 805 may be represented by all kinds of marks that the optical sensor 801 recognizes. For example, the reference point can be any marks printed on the biochip substrate 805, which the CCD camera can recognize.

The biochip array can dot the samples by using the established central position and the established coordinate system.

FIG. 9 is a plane view showing a biochip on which a reference point is indicated according to one preferred embodiment of the present invention.

Referring to FIG. 9, the reference points 803, 805, and 807 are recognized by the optical sensor 801, especially the image detecting element, is indicated at a predetermined position of the biochip substrate 805. In the preferred embodiment of the present invention, three reference points 803, 804, and 805 are indicated. The central reference point 803 is recognized as the central position and other reference points 804 and 805 can be set as the x-axis direction and the y-axis direction. The method for setting the x-axis direction and the y-axis direction and for setting each position of each spot will be described. The reference point can be indicated by means of a sample dotted onto the biochip substrate. For, example, the spot which functions as a reference spot can be set separately from the setting of other spots.

According to the method described with reference to FIGS. 8 and 9, when the reference point is indicated on the biochip substrate 805, the biochip arrayer can reset the central position and the coordinate system for the wrongly positioned biochip substrate 805 by using the optical sensor 801 though the biochip substrate 805 is wrongly positioned on the bed 107 (see FIG. 1), thereby always dotting the samples onto the correct predetermined positions on the biochip substrate 805.

The central control part 201 (see FIG. 2) installed in the biochip arrayer for setting the central position and the coordinate system will be described.

FIG. 10A is a flow chart illustrating a method for respotting a biochip arrayer by using an optical sensor according to one preferred embodiment of the present invention

and FIG. 10B is a schematic plane view illustrating a reference point according to one preferred embodiment of the present invention.

As shown in FIG. 10A and FIG. 10B, the reference point previously indicated on the biochip substrate is recognized by means of the optical sensor (step 1001). The indication of the reference point can be accomplished by the method described in FIG. 10B. Of course, other indications of the reference point are possible for indicating the central position and the coordinate system settings.

Reference positions R1 803, R2 807 and R3 805 corresponding to the reference point are calculated (step 1003).

A home position coordinate, an x-axis direction vector and a y-axis direction vector are calculated by using the reference positions R1 803, R2 807 and R3 805 (step 1005).

The x-axis coordinate of the home position Ox and the y-axis coordinate of the home position Oy are respectively obtained according to the following equations (1) and (2).

$$Ox=R1.x \text{ ------------------------------} (1)$$

$$Oy=R1.y \text{ ------------------------------} (2)$$

The x-axis direction unit vector Ex and the y-axis direction unit vector Ey are calculated according to the following equations (3) and (4).

$$Ex = \frac{R3 - R1}{|R3 - R1|} \text{ ---------------------} (3)$$

$$Ey = \frac{R2 - R1}{|R2 - R1|} \text{----------------------(4)}$$

With the calculated home position coordinate, the x-axis direction unit vector Ex and the y-axis direction unit vector Ey, the real coordinates Px and Py are calculated on the array of the spot position X and Y according to the following equations (5) and (6).

$$Px = Ox + X*Ex \text{----------------(5)}$$

$$Py = Oy + Y*Ey \text{-----------------(6)}$$

Preferably, the reference point and the spot position X, Y can be configured into the biochip arrayer for the manufacturer and the biochip arrayer for the user as previously promised. That is, the pattern of the spot can be configured into the biochip arrayer for the manufacturer and the biochip arrayer for the user as previously promised.

In another embodiment of the present invention, the pattern of the spot can be preset in the biochip arrayer for the manufacturer and recognized in the biochip arrayer for the user without manually configuring the pattern of the spot in the biochip arrayer for the manufacturer and the biochip arrayer for the user as previously promised.

In still another embodiment of the present invention, each pattern of each spot can be set in the biochip arrayer for the manufacturer, and then recognized in the biochip arrayer for the user.

Then, each motor is controlled in the step 1011 after each numerical control code is

generated for controlling each motor in the step 1009.

A precise respot is possible on the biochip substrate if the above-mentioned steps are implemented.

FIG. 11 is a flow chart illustrating a method for manufacturing a high precision biochip with a high precision and intellectual biochip arrayer by recognizing a biochip identifier according to one preferred embodiment of the present invention. The biochip can be manufactured by means of the controlling the central control part 201.

At first, the biochip identifier indicated on a portion of the biochip substrate is recognized (step 1101). Preferably, the biochip identifier can be composed of bar codes. The bar codes can include a one-dimensional bar code, a two-dimensional bar code or a three-dimensional bar code.

In the step 1103, the biochip information corresponding to the biochip identifier recognized in the step 1101 is extracted from the built-in database.

The database retrieving the biochip information will be described with reference to FIG. 12.

FIG. 12 is a schematic view illustrating a database retrieving biochip information corresponding to a biochip identifier according to one preferred embodiment of the present invention.

As shown in FIG. 12, the database retrieves various pieces of information such as the identifier 1201, the total number of spots 1203, the arrangement of the spots 1205, the

contents of the spots 1207, the sizes of the spots 1209, the intervals between the spots 1211, the position of the reference spot 1213 and the operation procedure of the biochip arrayer 1215.

It will be described as follows: the biochip identifier 1201 recognized from the bar code attached to the biochip substrate is '1'.

When the biochip identifier 1201 is recognized as '1', the biochip information corresponding to '1' includes the total number of spots 1203 as 100, the arrangement of the spots 1205 as HOR/ZIG, the content of the spot 1207 as HTBC, the size of the spot 1209 as 500μm, the interval of the spots 1211 as 1000μm, the position of the reference spot 1213 as (0, 0), (0, 10), (10, 0) and the operation procedure of the biochip arrayer 1215 as SUVSS.

In the arrangement of the spots 1205, HOR/ZIG means the configuration of spots in zigzags along the horizontal axis and VER/SEQ represents the configuration of the spots in order along the vertical axis.

In the contents of the spots 1207, HTBC represents HIV/HANTA/Hepaditis B/ Hepaditis C.

As for the operation procedure of the biochip arrayer 1215, S represents the spotting, U represents the ultrasonic washing and V represents the vacuum suction.

FIG. 13 is a plane view illustrating a method for calibrating a bed according to one preferred embodiment of the present invention.

Referring to FIG. 13, the first supporting point 1303 and the second supporting

point 1305 of the bed 107 adjust the height of the bed 107 and the y-axis direction. The third supporting point 1307 only adjusts the height of the bed 107. A screw adjusting part in FIGS. 14A and 14B supports each supporting point, and each supporting point is indicated as a point.

FIG. 14A is a cross-sectional view illustrating a method for adjusting the height of a third supporting point according to one preferred embodiment of the present invention.

Referring to FIG. 14A, the third supporting point 1307 adjusts the height of the bed 107 by adjusting the screw adjusting part 1403. The screw adjusting part 1403 can precisely adjust the inclined block with a screw.

FIG. 14B is a cross-sectional view illustrating a method for adjusting the heights and y-axis direction of a first and a second supporting points according to one preferred embodiment of the present invention.

Referring to FIG. 14B, the height of the bed 107 is adjusted at the first and the second supporting points 1303 and 1305 by adjusting the first screw adjusting part 1403. In addition, the y-axis direction of the bed 107 is adjusted at the first and the second supporting points 1303 and 1305 by adjusting the second screw adjusting part 1405. The first screw adjusting part 1403 precisely adjusts the inclined block with a screw. The y-axis direction of the bed 107 is adjusted by turning the end of the second screw adjusting part 1405 that has a round shape and the bed 107 contacts with the second screw adjusting part 1405 by means of a point contact.

The bed 107 is precisely calibrated according to the above-described method with reference to FIGS. 13, 14A and 14B.

FIG. 15 is a plane view illustrating a method for adjusting the y-axis direction of a bed according to one preferred embodiment of the present invention.

As shown in FIG. 15, the bed 107 is adjusted along the y-axis direction by identifying the y-coordinates the coordinates of the aligning bosses in the case that the coordinates of the aligning bosses of the first and the second substrate-retaining grooves 1501 and 1503 are (125, 25), (25, 25) when the number of the substrate-retaining grooves is two. Of course, the y-coordinates of the aligning bosses of the substrate retaining grooves are identified to adjust the bed in the y-axis direction when several substrate-retaining grooves exist.

To make a precise diagnosis in the biochip arrayer for the user, the diameter of the first spot dotted onto the biochip substrate in the biochip arrayer for the manufacturer should preferably different from the diameter of the second spot dotted onto the biochip substrate in the biochip arrayer for the user. The diameter of the first spot can be different from that of the second spot because the probe 103 (see FIG. 1) of the biochip arrayer for the manufacturer a different size than the size of the probe of the biochip arrayer for the user.

More preferably, the diameter of the first spot is larger than the diameter of the second spot. Hence, in the biochip reader including the CCD camera for detecting the

result of reactions that have occurred in the biochip substrate, the fluorescenin isothiocynate (FITC) for the CCD camera used to recognize the result of the reaction has a lower viscosity so that the deficiently in the FITC viscosity can be complemented. At that time, the first and the second spots respectively become the antigen and the antibody and the FITC is coated on the resultant antigen-antibody react, when the biochip substrate is the protein chip.

When the sample is dotted onto a biochip substrate, the biochip substrate is than the biochip.

While this invention has been described and shown as having multiple designs, the present invention may be further modified within the spirit and scope of this disclosure. This application is therefore intended to cover any variations, uses, or adaptations of the invention using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this invention pertains.

Industrial Applicability

According to the present invention, the biochip arrayer has a substrate-retaining groove enabling the biochip substrate to be aligned at the same position every time.

According to the present invention, the biochip arrayer can cope with the separation/combination of a protein chip and the movement of a protein chip.

According to the present invention, the biochip arrayer has an aligning boss formed on the substrate-retaining groove for setting the central position and the coordinate system of the biochip substrate.

According to the present invention, the biochip arrayer has a substrate-retaining stand including a plurality of substrate retaining grooves on which aligning bosses are formed in order to set the central positions and coordinates systems of a plurality of biochip substrates, respectively.

According to the present invention, the biochip arrayer has an optical sensor for recognizing predetermined reference points previously indicated on the biochip substrate so as to set the central position and the coordinate system of the biochip substrate.

According to the present invention, the biochip arrayer has the substrate-retaining stand which can be formed separately facilitating ease of maintenance and repair to the substrate retaining stand.

According to the present invention, the biochip arrayer has different spots for samples, thereby facilitating the simple diagnosis of samples.

According to the present invention, the biochip arrayer has the multiple spindle transfer system, thereby making the present invention applicable compatible with all types of biochips.

Claims

1. A biochip arrayer comprising:

a substrate-retaining stand having at least one substrate-retaining groove for holding a biochip substrate inserted into said substrate-retaining groove; and

a bed including at least one well plate retaining groove for fixing a well plate,

wherein said substrate-retaining groove comprises:

a first side for supporting said biochip substrate by two points or one line;

a second side for supporting said biochip substrate by one point or one line; and

an aligning boss for receiving a portion of said biochip substrate,

wherein said biochip substrate supported by the two points means said biochip's substrate is supported by two retaining protuberances that correspond to the two points and is formed at predetermined positions on said first side and wherein said biochip substrate is supported by the one points means said biochips substrate is supported by a retaining protuberance corresponded to the one point and formed at a predetermined position on said second side

2. The biochip arrayer as claimed in claim 1, wherein said first side substantially crosses at a right angle or a predetermined angle with said second side.

3. The biochip arrayer as claimed in claim 1, wherein said aligning boss is formed between said first side and said second side.

4. The biochip arrayer as claimed in claim 1, wherein said substrate retaining groove further comprises push portions respectively formed on a third side and a fourth side corresponding to said first side and said fourth side, respectively.

5. The biochip arrayer as claimed in claim 4, wherein said push portions respectively support said biochip substrate so that said biochip substrate is inserted and held in said substrate-retaining groove.

6. The biochip arrayer as claimed in claim 4, wherein said push portions are springs or elastic members, respectively.

7. The biochip arrayer as claimed in claim 6, wherein said push portions are composed of a plurality of springs or elastic members, respectively.

8. The biochip arrayer as claimed in claim 1, wherein said aligning boss has a central position for indicating a coordinate point on said biochip substrate.

9. The biochip arrayer as claimed in claim 8, wherein said central position is indicated by aligning a home position setting pin, a pin head and said aligning boss.

10. The biochip arrayer as claimed in claim 1, wherein said substrate retaining stand is combined separately with said bed.

11. The biochip arrayer as claimed in claim 1, wherein said bed further comprises a washing portion for washing a sample remaining on a probe or a container receiving the sample.

12. A method for dotting a biochip wherein a sample is dotted onto a biochip substrate on a biochip array in this case a first sample is the same size as a first spot and is previously dotted onto the biochip substrate using a biochip arrayer for a manufacturer, which comprises the steps of:

disposing a probe mounting part of a biochip arrayer for a user for dotting a second sample onto the first spot of said biochip substrate by using said biochip arrayer for the user; and

dotting the second sample onto a second spot corresponding to the second sample by using said biochip arrayer for the user, the second spot having a different size from the size of the first spot.

13. The method for dotting a biochip as claimed in claim 12, wherein the step of dotting the second sample onto the second spot is performed by adjusting a size of a second probe corresponding to the second spot to differ from a size of a first probe corresponding to the first spot so as to dot the second sample.

14. The method for dotting a biochip as claimed in claim 12, wherein the second spot is smaller than the first spot when the first spot is an antigen and the second spot is an antibody.

15. A method for manufacturing a biochip by using a biochip array comprising the steps of:

recognizing a biochip identifier indicated on a biochip substrate;

extracting biochip information corresponding to the biochip identifier from a built-in database wherein the biochip information includes at least one selected from the group consisting of total number of spots, alignment of the spots, contents of the spots, sizes of the spots, intervals between the spots, position of a reference spot and operating procedure of the biochip arrayer; and

dotting the contents of the spots onto the biochip substrate by using the biochip information.

16. The method for manufacturing the biochip as claimed in claim 15, wherein the biochip identifier is recognized from a bar code attached to the biochip substrate.

17. The method for manufacturing the biochip as claimed in claim 16, wherein the bar code is a first dimension bar code, a second dimension bar code or a third dimension bar code.

18. A biochip arrayer comprising:

an optical sensor for recognizing at least one reference point previously indicated on a biochip substrate;

a memory retrieving a program; and

a processor combined with said memory to execute the program,

wherein said processor executes in accordance with the program the step of setting a central position and a coordinate system of the biochip substrate to be retrieved by recognizing at least one reference point, and setting coordinates of spots to be retrieved by using the set central position and the coordinate system.

19. The biochip arrayer as claimed in claim 18, wherein the reference point

comprises a first reference point corresponding to the central position, a second reference point corresponding to an x-axis and a third reference point corresponding a y-axis.

20. The biochip arrayer as claimed in claim 18, wherein said optical sensor is an image detecting element or a position detecting element.

21. A biochip arrayer comprising:

an optical sensor for recognizing at least one reference point previously indicated on a biochip substrate;

a memory retrieving a program; and

a processor combined with said memory to execute the program,

wherein said processor executes in accordance with the program the step of :

setting a central position and a coordinate system of the biochip substrate to be retrieved by recognizing at least one reference point;

recognizing positions of spots by using the set central position, the coordinate system and coordinates of the spots wherein the coordinates of the spots are previously known; and

controlling dotting of samples in correspondence with the recognized positions of the spots.

22. The biochip arrayer as claimed in claim 21, wherein the reference point comprises a first reference point corresponding to the central position, a second reference point corresponding to an x-axis and a third reference point corresponding a y-axis.

23. The biochip arrayer as claimed in claim 21, wherein said optical sensor is an image detecting element or a position detecting element.

AMENDED CLAIMS
[received by the International Bureau on 8 February 2002 (08.02.02);
original claim 15 amended; remaining claims unchanged (1 page)]

13. The method for dotting a biochip as claimed in claim 12, wherein the step of dotting the second sample onto the second spot is performed by adjusting a size of a second probe corresponding to the second spot to differ from a size of a first probe corresponding to the first spot so as to dot the second sample.

14. The method for dotting a biochip as claimed in claim 12, wherein the second spot is smaller than the first spot when the first spot is an antigen and the second spot is an antibody.

15. A method for manufacturing a biochip by using a biochip arrayer comprising the steps of:

recognizing a biochip identifier indicated on a biochip substrate;

extracting biochip information corresponding to the biochip identifier from a built-in database wherein the biochip information includes at least one selected from the group consisting of total number of spots, alignment of the spots, contents of the spots, sizes of the spots, intervals between the spots, position of a reference spot and operating procedure of the biochip arrayer; and

dotting the contents of the spots onto the biochip substrate by using the biochip information.

FIG. 1

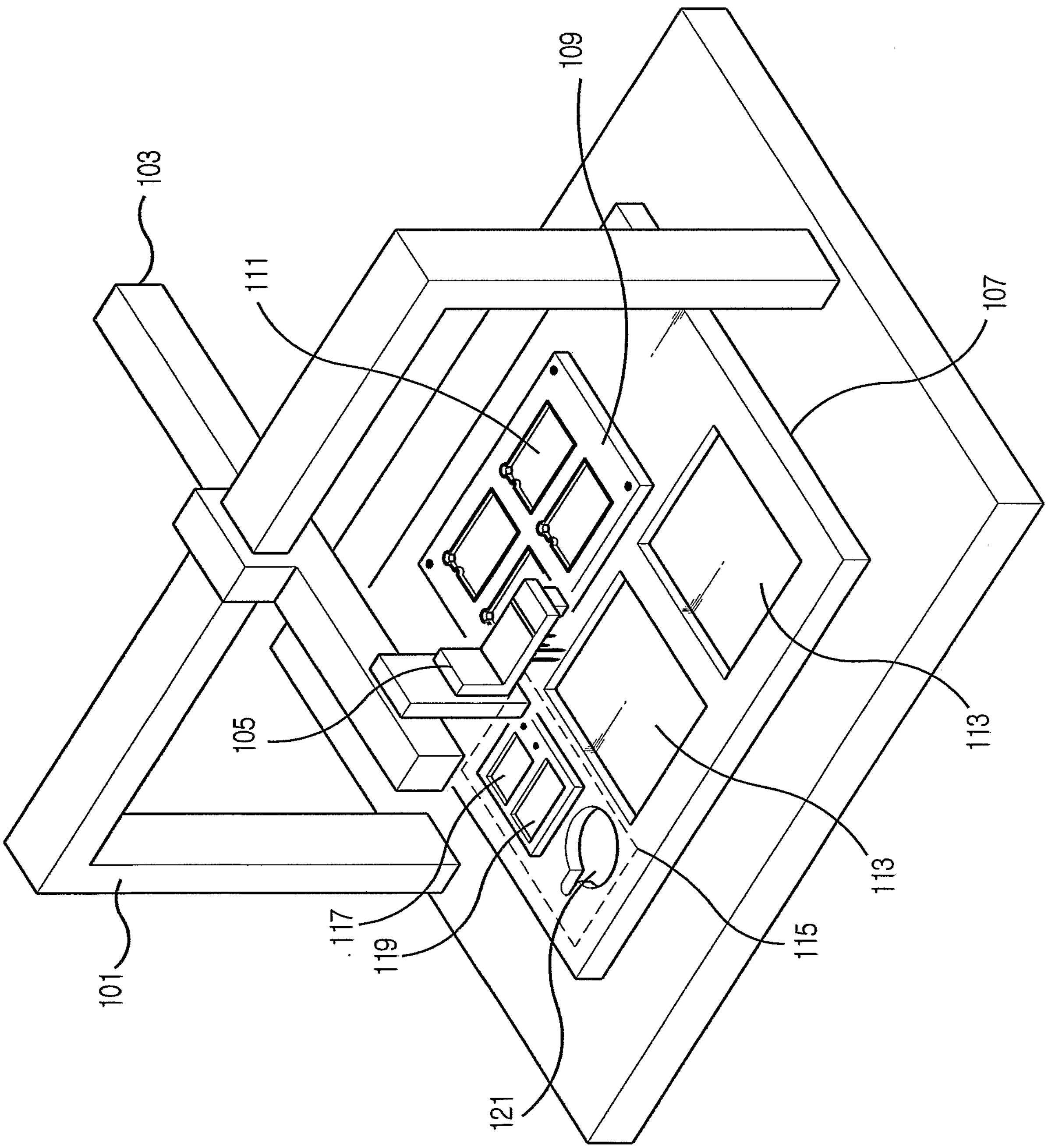


FIG. 2

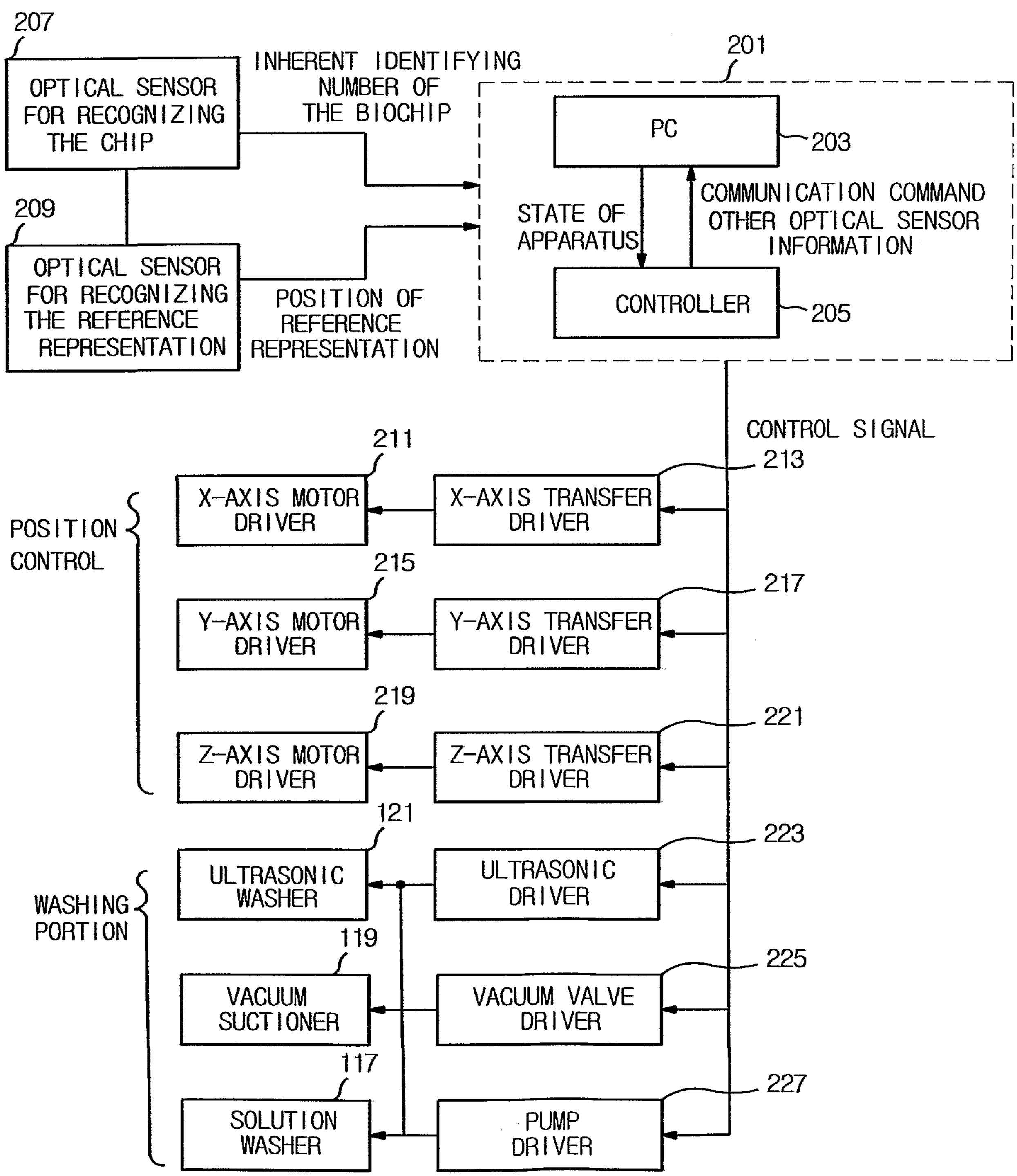

207
OPTICAL SENSOR FOR RECOGNIZING THE CHIP
INHERENT IDENTIFYING NUMBER OF THE BIOCHIP
209
OPTICAL SENSOR FOR RECOGNIZING THE REFERENCE REPRESENTATION
POSITION OF REFERENCE REPRESENTATION
201
PC
203
STATE OF APPARATUS
COMMUNICATION COMMAND OTHER OPTICAL SENSOR INFORMATION
CONTROLLER
205
CONTROL SIGNAL
POSITION CONTROL
211
X-AXIS MOTOR DRIVER
X-AXIS TRANSFER DRIVER
213
215
Y-AXIS MOTOR DRIVER
Y-AXIS TRANSFER DRIVER
217
219
Z-AXIS MOTOR DRIVER
Z-AXIS TRANSFER DRIVER
221
WASHING PORTION
121
ULTRASONIC WASHER
ULTRASONIC DRIVER
223
119
VACUUM SUCTIONER
VACUUM VALVE DRIVER
225
117
SOLUTION WASHER
PUMP DRIVER
227

FIG. 3

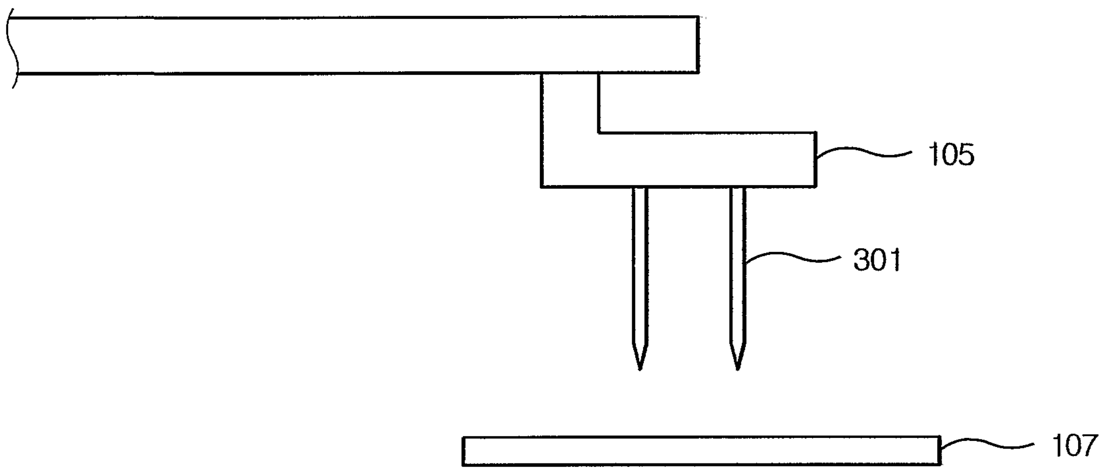


FIG. 4

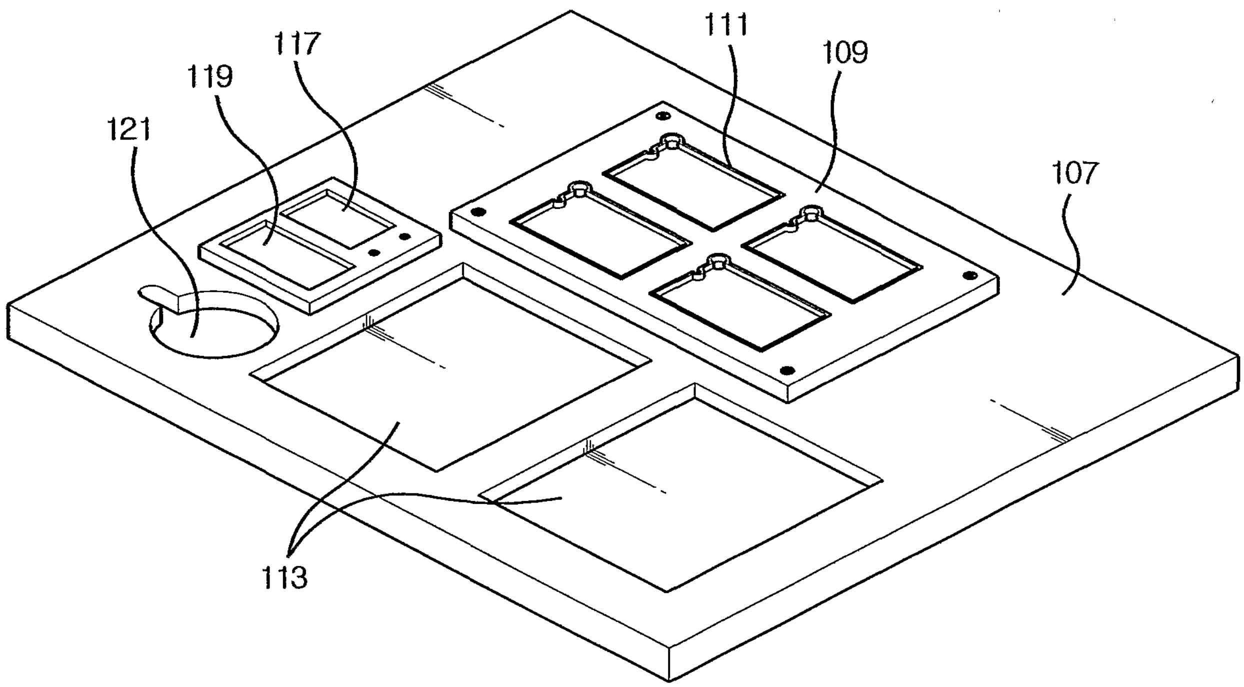


FIG. 5

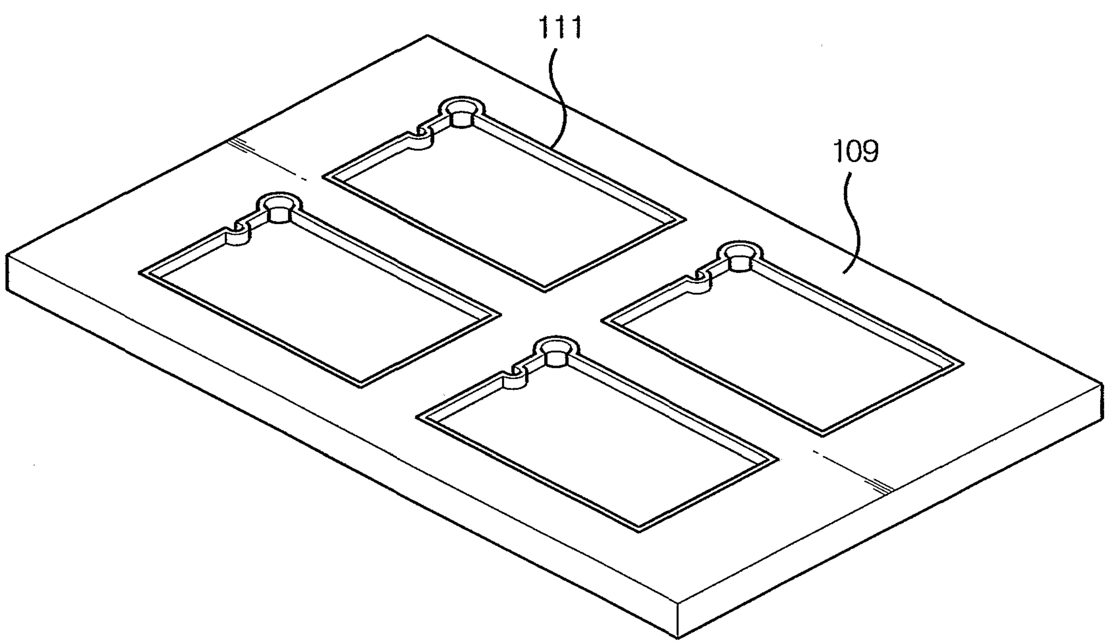


FIG. 6A

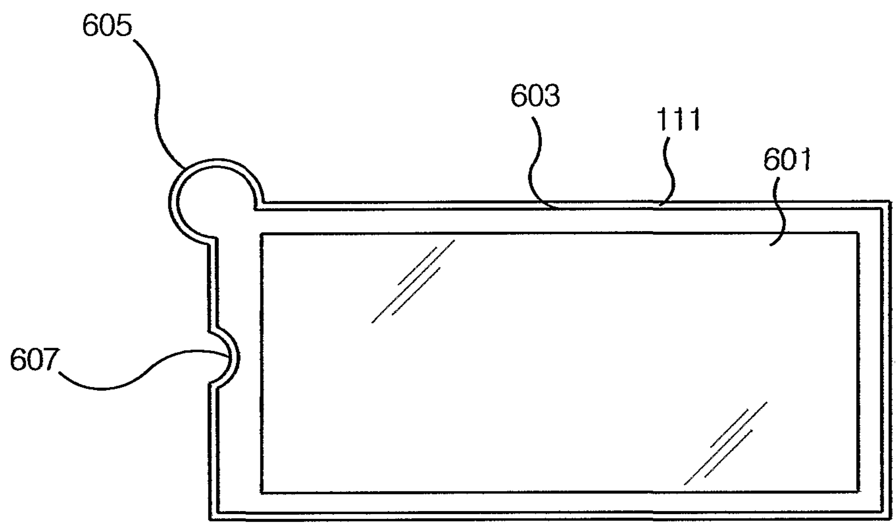


FIG. 6B

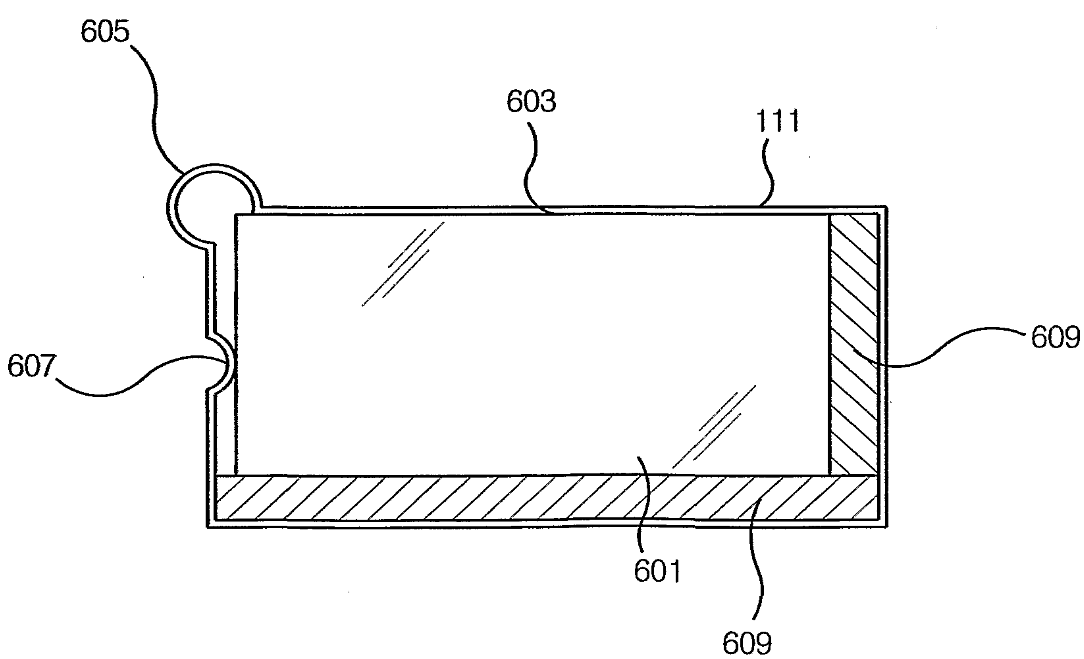


FIG. 6C

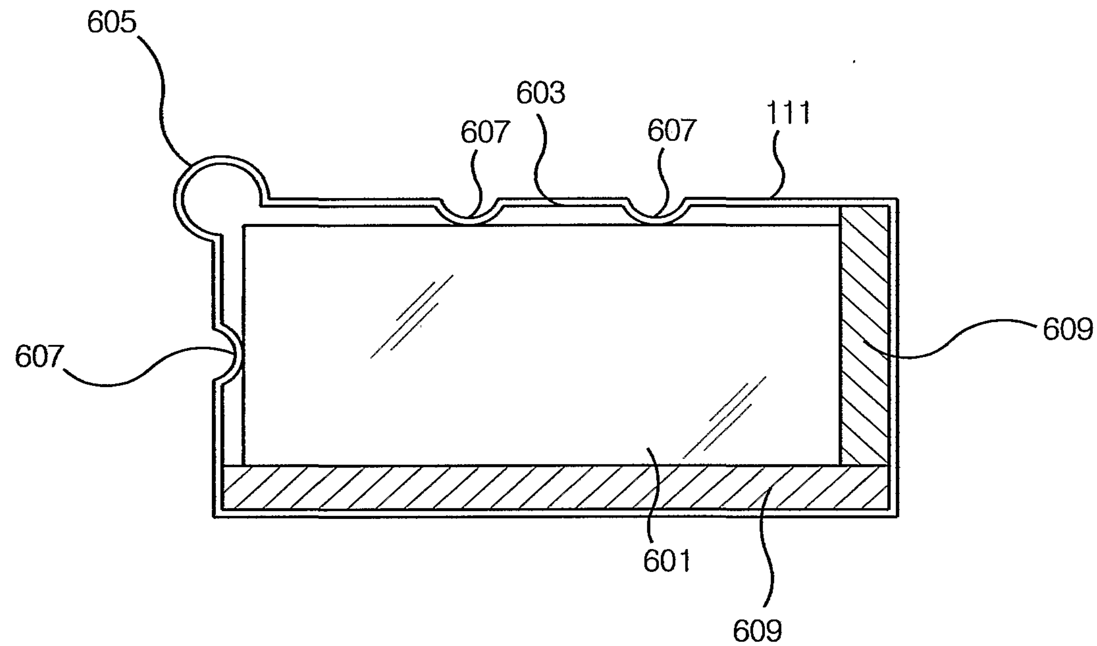


FIG. 6D

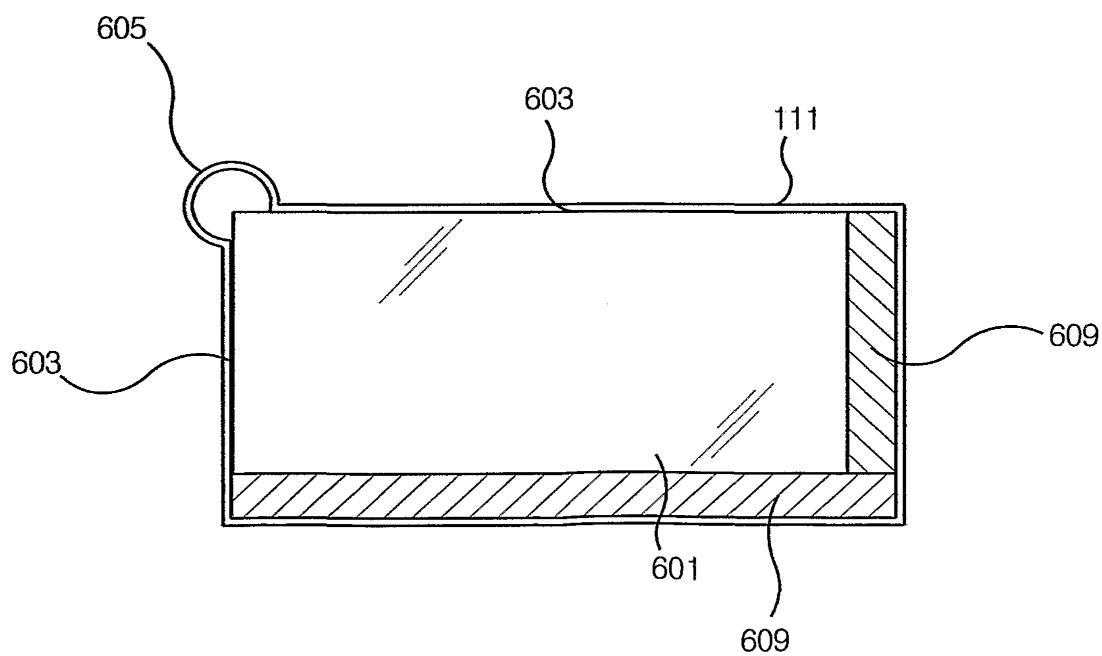


FIG. 6E

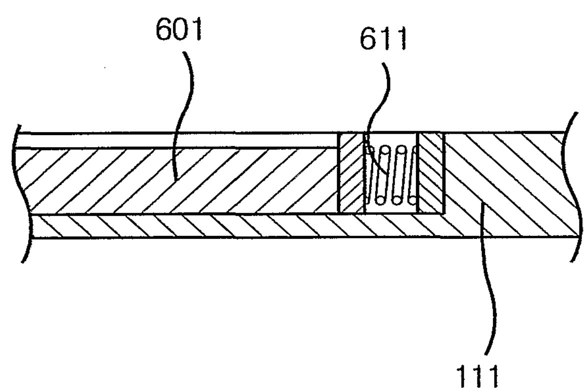


FIG. 6F

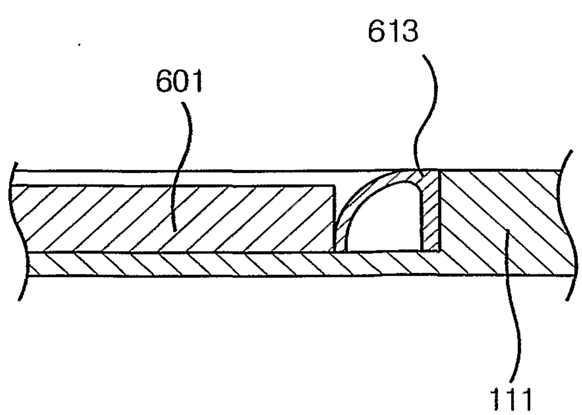


FIG. 7

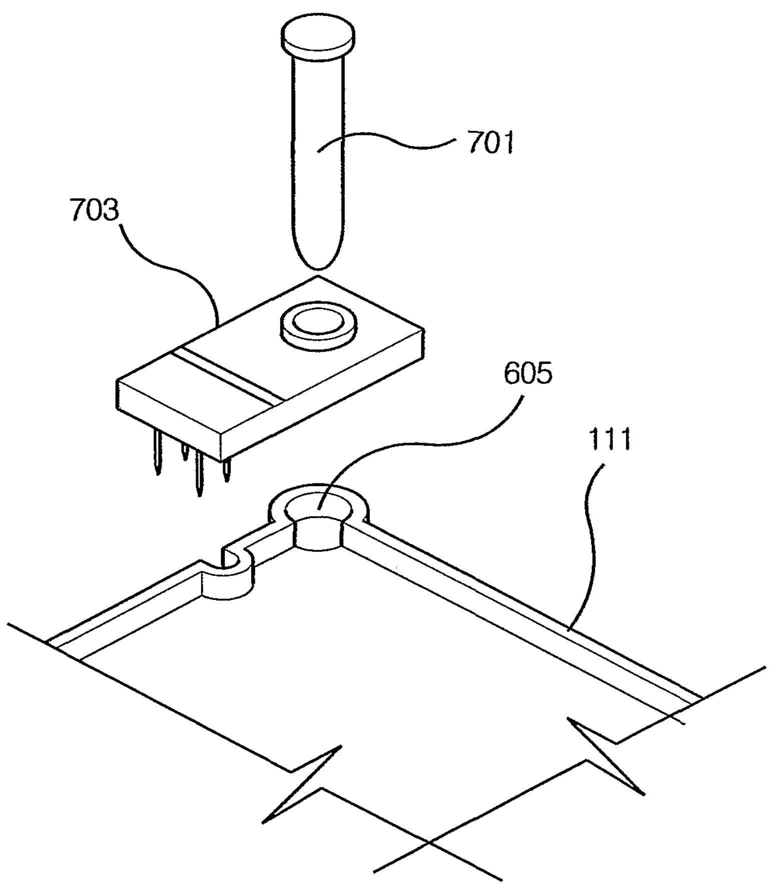


FIG. 8

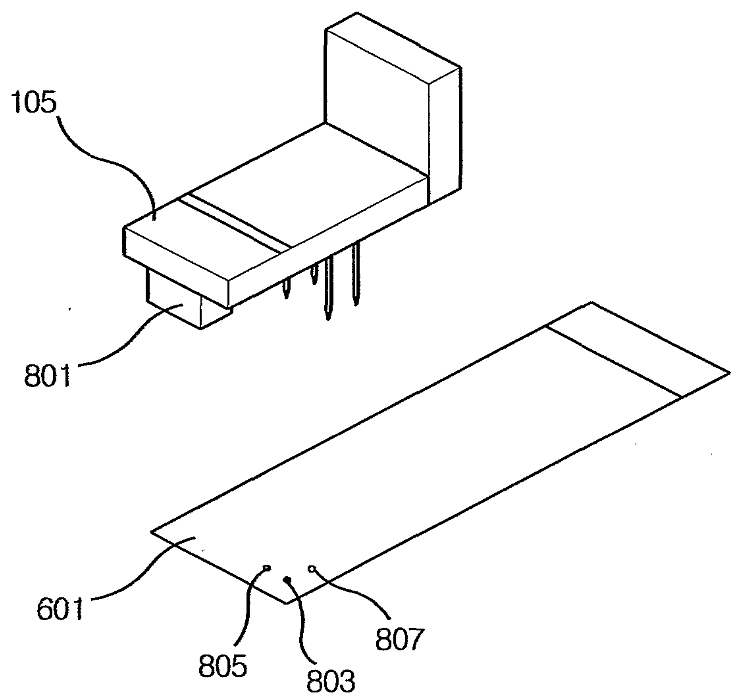


FIG. 9

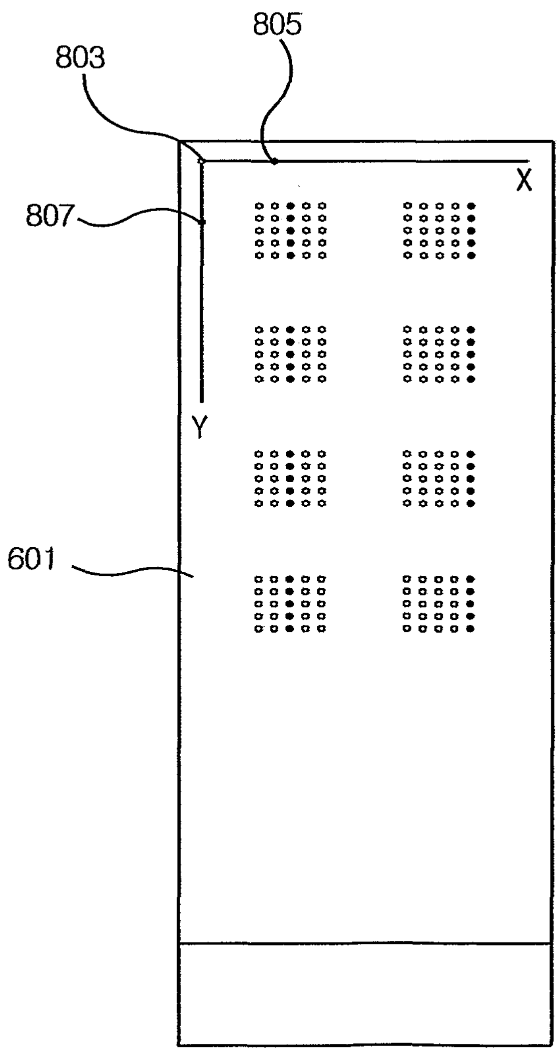


FIG. 10A

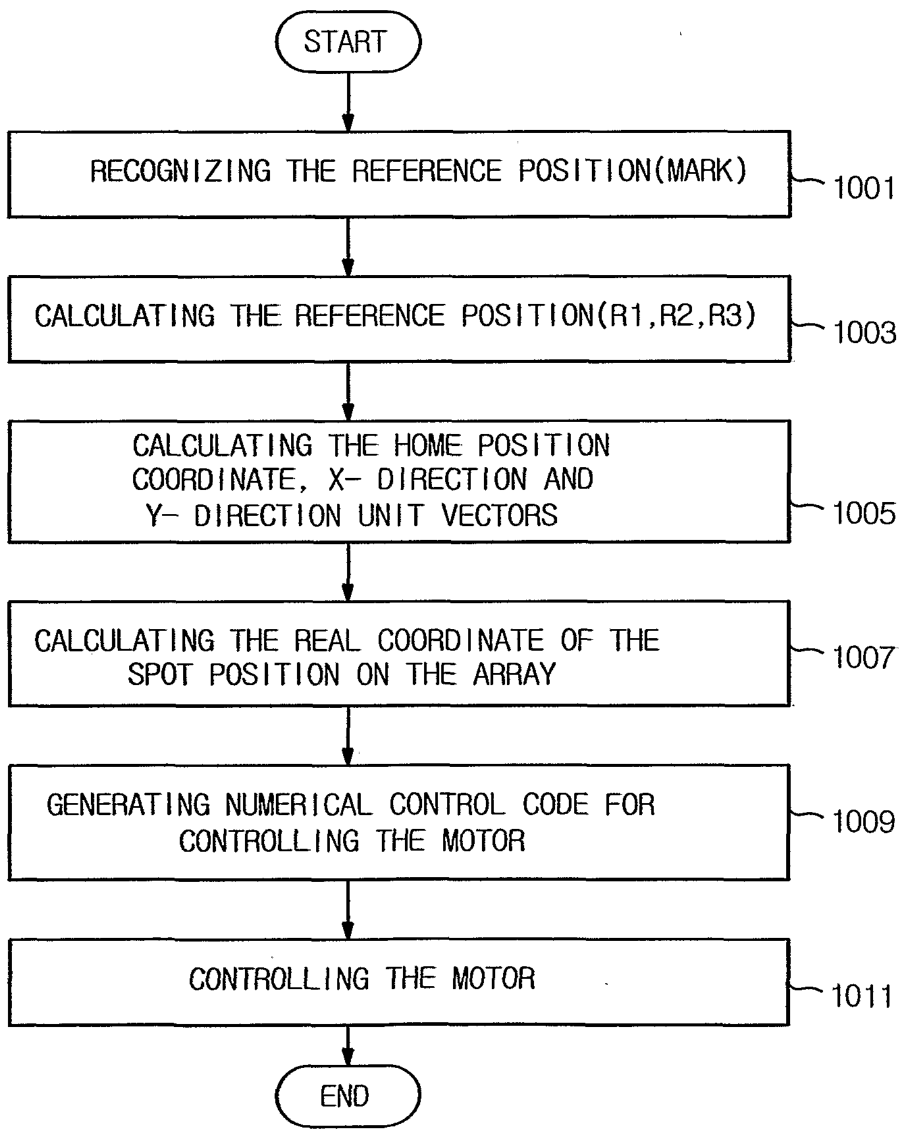

START
RECOGNIZING THE REFERENCE POSITION(MARK)
1001
CALCULATING THE REFERENCE POSITION(R1,R2,R3)
1003
CALCULATING THE HOME POSITION COORDINATE, X- DIRECTION AND Y- DIRECTION UNIT VECTORS
1005
CALCULATING THE REAL COORDINATE OF THE SPOT POSITION ON THE ARRAY
1007
GENERATING NUMERICAL CONTROL CODE FOR CONTROLLING THE MOTOR
1009
CONTROLLING THE MOTOR
1011
END

FIG. 10B

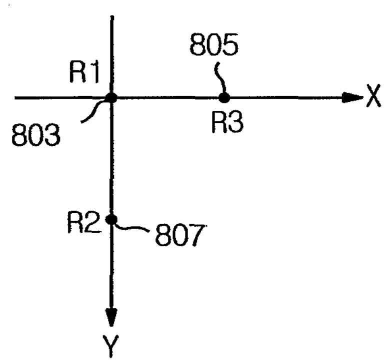


FIG. 11

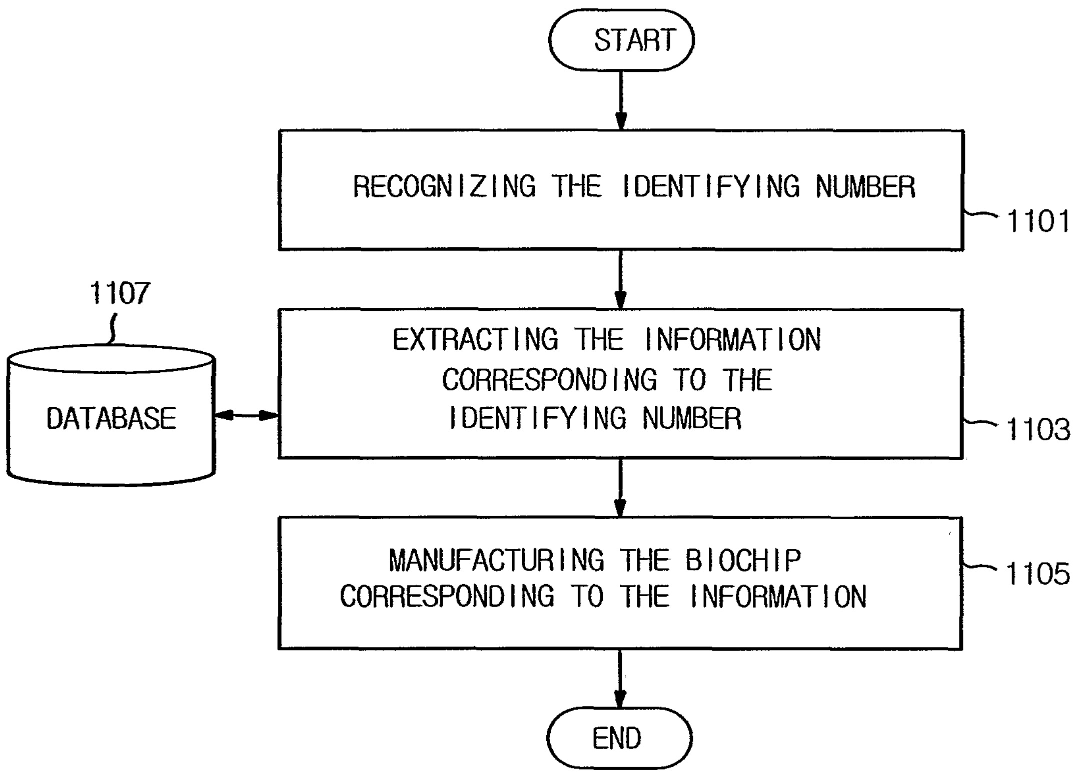

START
RECOGNIZING THE IDENTIFYING NUMBER
1101
1107
DATABASE
EXTRACTING THE INFORMATION CORRESPONDING TO THE IDENTIFYING NUMBER
1103
MANUFACTURING THE BIOCHIP CORRESPONDING TO THE INFORMATION
1105
END

FIG. 12

1201	1203	1205	1207	1209	1211	1213	1215
IDENT-IFIER	TOTAL NUMBER OF SPOTS	ARRANGEMENT OF SPOTS	CONTENTS OF SPOTS	SIZES OF SPOTS	INTERVALS AMONG SPOTS	POSITION OF REFERENCE SPOTS	OPERATION PROCEDURE OF ARRAYER
1	100	HOR/ZIG	HTBC	500 μm	1000 μm	(0,0),(0,10),(10,0)	SUVSS
2	100	VER/SEQ	TCBH	300 μm	1000 μm	(0,0),(0,10),(10,0)	SSVSS
3	200	HOR/SEQ	BTHC	500 μm	500 μm	(0,0),(0,5),(5,0)	SUVSU
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

FIG. 13

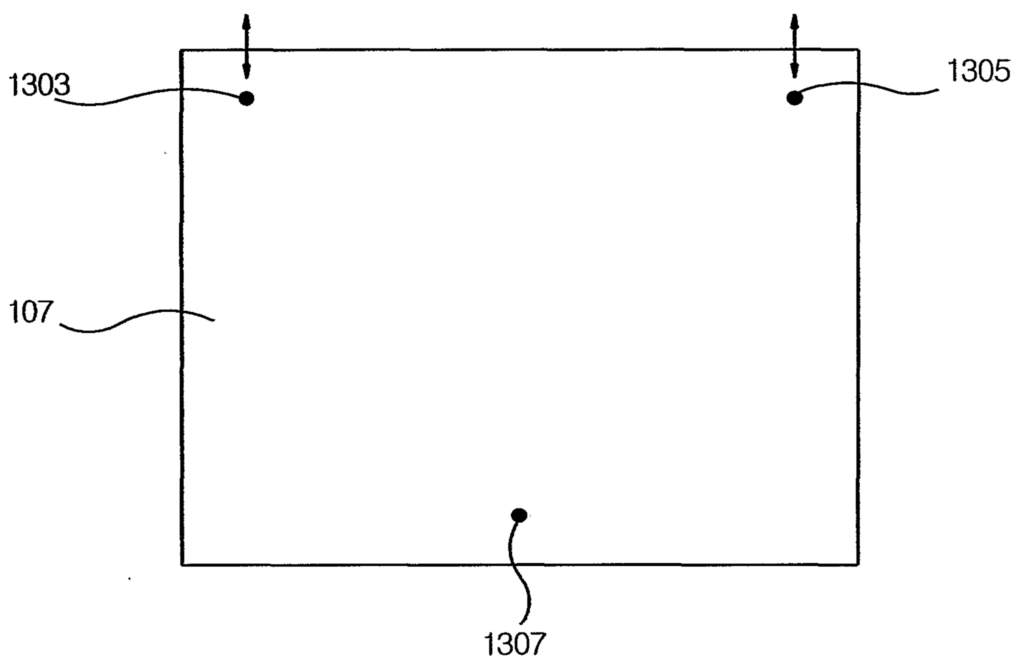


FIG. 14A

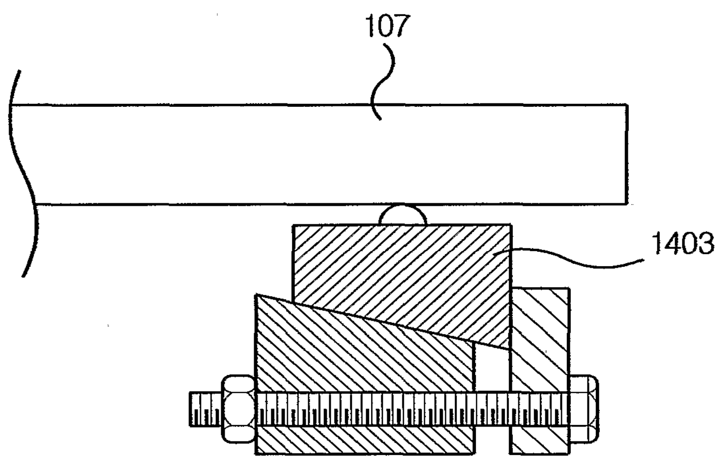


FIG. 14B

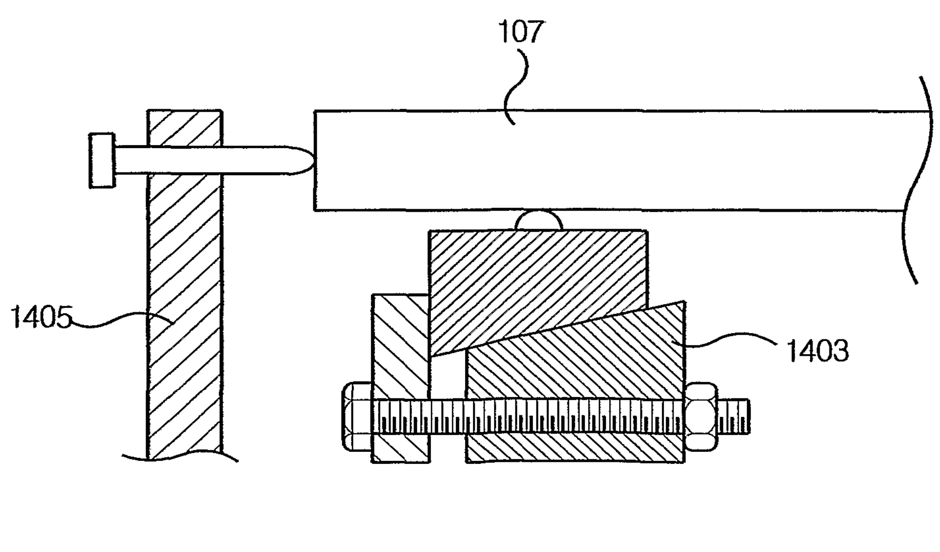
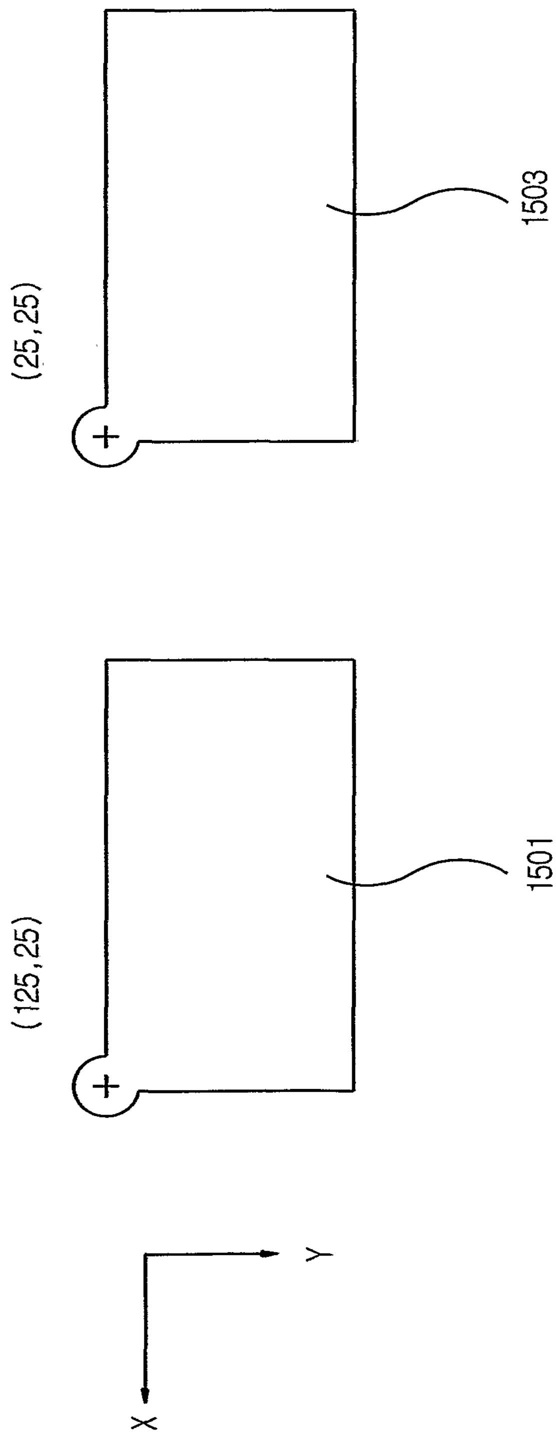


FIG. 15



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01200

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C12Q 1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
IPC7 C12Q 1/68

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched
Korean Patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
EspaceNet, IPDL(WIPO), USPTO, PAJ
"arrayer and (coordinate or axis)", "array* and align* and boss", "scan and (coordinate or axis) and optical and sensor"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/51058 A1 (General Scanning, Inc.) 25 February 2000	15 - 17
A	EP 99/8697 A (Affymetrix) 4 February 1999	15 - 17
A	US 5807522 (The Board of Trustees of the Leland Stanford Junior University) 15 September 1998	1 - 23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 AUGUST 2001 (22.08.2001)	17 SEPTEMBER 2001 (17.09.2001)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
HAN, Hyun Sook
Telephone No. 82-42-481-5596

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01200

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to part of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Search Authority found multiple inventions in this international application, as follows:

I. Claims 1-11 directed to a bio-chip arrayer comprising a substrate retaining stand with a plurality of substrate retaining grooves, wherein each substrate retaining groove includes a retaining edge, a retaining protuberance and a aligning boss.
II. Claims 12-14 directed to a dotting method of bio-chip comprising a dotting step of the second spot of the second sample on the first spot.
III. Claims 15-17 directed to a preparation method of bio-chip comprising a step recognizing an identifier on the substrate, a step extracting the information from the database established previously and a step dotting the spot using the information.
IV. Claims 18-23 directed to a bio-chip arrayer comprising a optical sensor recognizing at least one standard mark, memory comprising a program, processor executing the program.

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be established without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR00/01200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 00/51058 A1	25-02-2000	US 6215894 A	10-04-2001
EP 99/8697 A	04-02-1999	WO 99/5323 A	04-02-1999
		US 6188783 A	13-02-2001
US 5807522 A	15-09-1998	AU 2862995 A1	15-01-1996
		EP 97/804731 A	05-11-1997
		WO 95/35505 A	28-12-1995